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## RISK FACTORS FOR LARYNGEAL CANCER IN MONTENEGRO

Elvir ZVRKO<sup>1</sup>, Zorana GLEDOVIĆ<sup>2</sup>, and Agima LJALJEVIĆ<sup>3</sup>

*Clinic for Otorhinolaryngology and Maxillofacial Surgery, Clinical Centre of Montenegro, Podgorica, Montenegro<sup>1</sup>, Institute for Epidemiology, University of Belgrade School of Medicine, Belgrade, Serbia<sup>2</sup>, Institute of Public Health, Podgorica, Montenegro<sup>3</sup>*

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Laryngeal cancer is the most common head and neck cancer. There might be many risk factors for laryngeal cancer. Smoking, especially cigarette smoking and alcohol are indisputable risk factors. The authors of this paper assessed the presumed risk factors in order to identify possible aetiological agents of the disease.

A hospital-based case-control study was conducted. The study group consisted of 108 histologically verified laryngeal cancer patients and 108 hospital controls matched by sex, age ( $\pm 3$  years) and place of residence. Laryngeal cancer patients and controls were interviewed during their hospital stay using a structured questionnaire. According to multiple logistic regression analysis six variables were independently related to laryngeal cancer: hard liquor consumption (Odd Ratio /OR/=2.93, Confidence Interval /CI/ 95 % = 1.17 to 7.31), consumption more than 2 alcoholic drinks per day (OR=4.96, CI 95 % = 2.04 to 12.04), cigarette smoking for more than 40 years (OR=4.32, CI 95 % = 1.69 to 11.06), smoking more than 30 cigarettes per day (OR=4.24, CI 95 % = 1.75 to 10.27), coffee consumption more than 5 cups per day (OR=4.52, CI 95 % = 1.01 to 20.12) and carbonated beverage consumption (OR=0.38, CI 95 % = 0.16 to 0.92).

The great majority of laryngeal cancers could be prevented by eliminating tobacco smoking and alcohol consumption.

**KEY WORDS:** *alcohol, carbonated beverages, case-control study, coffee, larynx, tobacco smoking*

Laryngeal cancer is the most common head and neck cancer (excluding skin cancer). Squamous cell carcinoma is the most common histological type of laryngeal malignancy. It accounts for more than 90 % of laryngeal cancers in most studies (1, 2). Most patients are 50 to 75 years of age at presentation. Laryngeal cancer is the neoplasm with the largest male to female sex ratio in most populations. It ranges from 4:1 to 20:1 between countries, but most common ranges are from 6:1 to 10:1 (3-5).

There might be many risk factors for laryngeal cancer. Smoking, especially cigarette smoking and alcohol are indisputable risk factors and act synergistically to increase the risk of malignant transformation (6). Other factors associated with

increased risk of laryngeal cancer include prolonged exposure to fossil fuels (7), human papillomavirus infections (8, 9), chronic gastro-oesophageal reflux (10), passive smoking (11), and occupational exposure to substances such as asbestos, wood, cement, solvents, nickel (12-15). Those working in the railway and lumber industry, sheet-metal workers, grinding-wheel operators, and car mechanics are also said to have a higher incidence of laryngeal cancer (16). Other factors of interest are dietary factors, such as a low keratin intake. High dietary intake of fruits and vegetables is associated with a decreased incidence of laryngeal cancer, possibly because of a protective effect related to high contents of vitamins A and C (17).

The authors of this paper assessed the presumed risk factors in order to identify possible aetiological agents of the disease.

## MATERIAL AND METHODS

A hospital-based case-control study was conducted. The study group consisted of 108 histologically verified laryngeal cancer patients and 108 hospital controls matched by sex, age ( $\pm 3$  years) and place of residence. All laryngeal cancer patients were diagnosed and treated at the Clinic for Otorhinolaryngology and Maxillofacial Surgery of the Clinical Centre of Montenegro in Podgorica between January 2001 and June 2003. Controls were recruited among patients admitted to different Centre clinics for a wide spectrum of acute, non-malignant conditions, unrelated to smoking and alcohol consumption. Twenty-seven percent of the controls were admitted for non-alcoholic-related traumas, 13 % for other orthopaedic disorders, 15 % for acute surgical conditions, and 45 % for miscellaneous other illnesses, including eye, nose, ear or skin disorders. The response rate was 94 % for both laryngeal cancer patients and controls.

Laryngeal cancer patients and controls were interviewed during their hospital stay using a structured questionnaire administered by one study doctor. The exact site and extent of the primary disease were recorded on the basis of the initial clinical description and staging investigations according to the sixth edition of the 2002 TNM classification agreed upon by the Union Against Cancer and the American Joint Committee on Cancer (18).

The following variables were tested for their association with laryngeal cancer: sociodemographic characteristics (sex, age, profession, educational level, housing quality, vicinity of industrial area), unfavourable working conditions (long-term exposure to low/high temperature, sudden and frequent temperature changes at work, exposure to passive smoking, metal and non-metallic mineral, chemical, petroleum, coal, rubber, plastics, wood and paper manufacturing and processing), lifestyle habits (tobacco smoking, alcohol consumption, coffee consumption, diet), loud speech at work, personal medical history (tuberculosis, bacterial and viral infections of the respiratory tract, frequent hoarseness, persistent cough, tonsillectomy and laryngeal surgery), and family history of cancer in first-degree relatives.

The section on smoking habits included questions on smoking status (never, ex-, or current smokers), daily number of cigarettes ( $\leq 20$ , 21-30, 31-40,  $> 40$ ), starting age ( $< 16$ , 16-20,  $> 20$ ) and quitting age. Ever smokers were subjects who had smoked at least one cigarette per day for at least 1 year. Ex-smokers had abstained from any type of smoking for at least 12 months.

Taking into account different ethanol concentration, one alcohol drink corresponded to approximately 125 mL of wine, 330 mL of beer, and 30 mL of hard liquor (i.e. about 12 g of ethanol). Never drinkers were individuals who had abstained from any alcohol beverage lifelong. Ex-drinkers had abstained from any type of alcohol for at least 12 months. Information on starting age and, for ex-drinkers, quitting age was also recorded.

### *Data analysis*

All patient record data were re-evaluated by the same otorhinolaryngologist and transferred into a database. The statistical analyses were carried out using SPSS 11.5 for Windows. Differences in proportions were analysed by the means of the chi-square test and Fisher's exact test. A p-value of less than 0.05 was considered statistically significant. In order to estimate the independent, unconfounded effect of the risk factors, multivariable logistic regression analysis was applied. All factors found to be related to laryngeal cancer according to the chi-square test and Fisher's exact test were considered for inclusion in the logistic regression model. The 95 % confidence interval (CI) of odds ratio (OR) was reported to show the precision of estimation. Alcohol and smoking were accounted for in all analyses.

## RESULTS

The age of the 108 laryngeal cancer patients ranged from 39 to 83 years [mean  $\pm$  SD = (59.9  $\pm$  9.7) years, median = 60 years]. There were 88 (81.5 %) male and 20 (18.5 %) female patients, and the male:female ratio was 4.4:1. The median age of men at the time of diagnosis was 60 years (range 39 to 82 years) and that of women 62.5 years (range 42 to 83 years). Most patients were affected in their sixth and seventh decades of life. There were 69.4 % patients in the age group of 51 to 70 years. Education level of the laryngeal cancer patients varied and most of

them were urban dwellers. The urban:rural population ratio was 2.9:1. The age of the 108 controls ranged from 38 to 85 years [mean±SD=(59.5±10.2) years, median=59.5 years]. The distribution of laryngeal cancer patients and controls according to age, sex, and place of residence is shown in Table 1.

**Table 1** Distribution of 108 laryngeal cancer patients and 108 controls according to selected variables

Variable	Patients/ number	Controls/ number
<b>Age / years</b>		
35 to 45	7	8
46 to 55	32	32
56 to 65	37	37
66 to 75	26	26
76 to 85	6	5
<b>Sex</b>		
Male	88	88
Female	20	20
<b>Residence</b>		
Urban area	80	80
Rural area	28	28
Total	108	108

Fifty-eight patients had a supraglottic tumour (53.7 %) and 50 had a glottic tumor. There were no cases of subglottic cancer. Twenty-two patients with glottic and five with supraglottic cancer had stage I tumour. All 11 stage IV cancers were supraglottic. In 103 (95.4 %) patients the histological finding was squamous cell carcinoma, in one (0.93 %) adenocarcinoma, and in four (3.7 %) carcinoma in situ. Of the 103 squamous cell carcinomas with the histological grade available, 65 (63.1 %) were well, 33 (32 %) moderately, and five (4.9 %) poorly differentiated. Table 2 shows the tumour characteristics of the laryngeal cancer group.

According to the chi-square test and Fisher's exact test, only 24 variables were significantly related to laryngeal cancer (Table 3). All of these variables entered the model of conditional regression analysis.

Laryngeal cancer was strongly associated with cigarette smoking (OR=15.09, p=0.000). Ninety-seven patients (89.8 %) were smokers and six were ex-smokers (5.5 %). We found a statistically significant difference for cigarette smoking for over 20 years, 30

**Table 2** Tumour characteristics of the study group

	Male	Female	Total
<b>Site</b>			
Glottic	41	9	50
Supraglottic	47	11	58
<b>T category</b>			
Tis	3	1	4
T1	21	6	27
T2	52	10	62
T3	7	3	10
T4a	5		5
<b>N category</b>			
N0	79	19	98
N1	4	1	5
N2	5		5
<b>Stadium</b>			
0	3	1	4
I	21	6	27
II	44	9	53
III	9	4	13
IVa	10		10
IVc	1		1

years and 40 years, for smoking over 20 cigarettes per day, 30 cigarettes per day, and 40 cigarettes per day, and for the starting age before 21 years. Passive smoking was also a risk factor for laryngeal cancer (OR=4.47, p=0.000).

Concerning regular alcohol consumption there were significant differences between laryngeal cancer patients and controls in hard liquor consumption, alcohol consumption for over 40 years, consumption of more than two alcoholic drinks per day, and consumption of more than four alcoholic drinks per day. Eighty-nine laryngeal cancer patients (82.41 %) admitted to have drunk alcohol. There was no statistically significant difference between laryngeal cancer patients and controls in wine and beer consumption.

A significant association was found between laryngeal cancer and unfavourable working conditions, meat and processed meat consumption, salty diet, and frequent hoarseness prior to disease. Malignant tumours in the first-degree relatives were also significantly more frequent in laryngeal cancer patients than in controls.

An inverse relation was found for fruit and vegetable consumption (OR=0.28, p=0.020) and carbonated beverage consumption (OR=0.51, p=0.014).

Table 3 Risk factors for laryngeal cancer: chi-square test and Fisher's exact test

Risk factor	Odds ratio (OR)	95 % confidence interval (CI)	p-value
Long term unfavourable working conditions	1.90	1.10-3.28	0.020
Meat and processed meat consumption	2.05	1.19-3.53	0.009
Fruit and vegetable consumption	0.28	0.09-0.89	0.020
Salty diet	1.88	1.08-3.27	0.026
Carbonated beverage consumption	0.51	0.29-0.88	0.014
Alcohol consumption for over 40 years	2.43	1.07-5.50	0.030
Alcohol consumption more than 2 drinks per day	2.79	1.10-7.07	0.026
Alcohol consumption more than 4 drinks per day	5.45	2.84-10.45	0.000
Hard liquor consumption	1.89	1.02-3.51	0.043
Coffee consumption	3.32	1.16-9.49	0.019
Coffee consumption for over 40 years	2.68	1.25-5.74	0.010
Coffee consumption more than 2 cups per day	2.48	1.39-4.39	0.002
Coffee consumption more than 5 cups per day	5.72	2.09-15.61	0.000
Regular cigarette smoking	15.09	5.54-41.08	0.000
Age at start smoking: before 21 years	1.95	1.05-3.60	0.032
Smoking for over 20 years	2.56	1.04-6.28	0.036
Smoking for over 30 years	3.10	1.66-5.78	0.000
Smoking for over 40 years	4.44	2.18-9.04	0.000
Smoking over 20 cigarettes per day	2.26	1.02-5.01	0.041
Smoking over 30 cigarettes per day	3.18	1.67-6.08	0.000
Smoking over 40 cigarettes per day	4.17	2.19-7.91	0.000
Passive smoking	4.47	2.49-8.05	0.000
Frequent hoarseness	3.09	1.45-6.58	0.003
Cancer in first-degree relatives	2.66	1.23-5.72	0.011

Table 4 Risk factors for laryngeal cancer: multiple logistic regression analysis

Risk factor	p-value	Odds ratio (OR)	95 % confidence interval (CI)
Carbonated beverages consumption	0.032	0.38	0.16-0.92
Consumption more than 2 alcoholic drinks per day	0.000	4.96	2.04-12.04
Hard liquor consumption	0.021	2.93	1.17-7.31
Coffee consumption more than 5 drinks per day	0.048	4.52	1.01-20.12
Cigarette smoking for over 40 years	0.002	4.32	1.69-11.06
Smoking more than 30 cigarettes per day	0.001	4.24	1.75-10.27

According to multiple logistic regression analysis, six variables were independently related to laryngeal cancer (Table 4): hard liquor consumption (OR=2.93), consumption of more than two alcoholic drinks per day (OR=4.96), cigarette smoking for more than 40

years (OR=4.32), smoking over 30 cigarettes per day (OR=4.24), coffee consumption of more than five cups per day (OR=4.52), and carbonated beverage consumption (OR=0.38).

## DISCUSSION

The aetiology of laryngeal cancer remains unknown. In addition to tobacco and ethanol, the current multifactorial hypothesis of laryngeal cancer suggests that other risk factors may also influence carcinogenesis. It is supported by a phenomenon of multicentric mucosal carcinoma known as *field cancerisation*.

Cigarette smoking is considered to be the most important risk factor for laryngeal cancer. A vast majority (88 % to 98 %) of patients with laryngeal carcinoma are smokers (19-21). Approximately 87 % of laryngeal cancer cases in Central Europe are attributable to tobacco use, of which 75 % and 12 % are due to current and past smoking, respectively (22). The carcinogenic effect of tobacco smoke correlates with the intensity and duration of smoking (3, 15, 22-24). In a study performed by Sokić et al. (12) the OR for smoking for more than 10 years was 7.29. Falk et al. (25) observed a dose-dependent relationship between smoking and laryngeal squamous cell carcinoma. The relative risk was 4.4-fold for patients who smoked up to half-a-pack per day, and 10.4-fold for those smoking more than two packs per day. Our data show that current smokers run about 15 times higher risk of laryngeal cancer than never-smokers. Furthermore, the number of cigarettes and duration of smoking were strongly related to laryngeal cancer risk. It seems that the effect of smoking is more important for the supraglottic than glottic cancer (22).

The importance of alcohol as a risk factor for laryngeal cancer has been consistently reported in several studies (26, 27). In our study, the relation between alcohol and laryngeal cancer was weaker than between laryngeal cancer and smoking. Experimental studies have not implicated alcohol itself as a carcinogen, but ethanol is the main component of alcoholic beverages that determines the risk of cancer. Alcohol may promote carcinogenesis by a variety of mechanisms: nutritional deficiencies associated with heavy drinking, the effects of contaminants in alcoholic beverages, the induction of microsomal enzymes that enhance the metabolic activation of tobacco or other carcinogens, and the capacity of alcohol to solubilize carcinogens or enhance their penetration in laryngeal tissues (28, 29). Wine is the beverage most strongly related to the risk of laryngeal cancer in Italy (30). However, in our study the significant risk was found for hard liquor consumption. There is no evidence that the effect depends on the type of alcoholic beverage

and the most frequently consumed beverages, in each area, tend to be the ones with the highest risk (6, 31). Alcohol seems to be more significant in the aetiology of the supraglottic than glottic cancer, and its carcinogenic effect is also dose-dependent (6, 32, 33). Koskinen et al. (34) in their prospective multi-centre study found that heavy alcohol drinking was associated with an increased risk of death, advanced-stage disease, and younger age at diagnosis.

Dietary factors such as low fruit and vegetable intake and consumption of salted meat and fish have been associated with elevated laryngeal cancer risk (17, 19, 26, 35, 36). According to our results, only consumption of carbonated beverages is independently related to laryngeal cancer. Carbonated beverage consumption was inversely associated with laryngeal cancer in our study. This protective effect is questionable and a likely explanation is that patients with laryngeal cancer drink more alcoholic beverages than carbonated beverages, whereas in the control group the tendency is opposite. Further studies should be able to ascertain if this is true.

Meat and processed meat consumption (OR=2.05,  $p=0.009$ ) and salty diet (OR=1.88,  $p=0.026$ ) were identified as the risk factors for laryngeal cancer, but only according to Fisher's test. This test also identified fruit and vegetable consumption as protective factors (OR=0.28,  $p=0.020$ ).

Coffee consumption and cancer risk have mainly been evaluated for cancers of the urinary bladder, pancreas, colon and rectum (37). In most studies, the risk of bladder cancer tends to be higher in coffee drinkers than in those who do not drink coffee, but the excess risk is generally moderate and is neither dose- nor duration-related. De Stefani et al. (38) found in Uruguay that coffee and tea were strongly associated with bladder cancer risk, and their results suggest that coffee consumption may be a risk factor for bladder carcinoma. Larsson et al. (39) prospectively investigated the association between long-term coffee consumption and the risk of stomach cancer in a population-based cohort study, and found that coffee consumption increased the risk of stomach cancer in a dose-dependent manner. Botelho et al. performed a meta-analysis, and found no adverse effects of coffee associated with gastric cancer (40). Investigation of other cancer sites has been less extensive. We found that regular daily consumption of more than five cups of coffee is an independent risk of laryngeal cancer, but our finding needs to be confirmed by other prospective studies. It would

be very interesting to see the incidence of laryngeal cancer in non-smokers and non-coffee consumers, but there were only five (4.6 %) non-smoking patients with laryngeal cancer in our study and only two had never drunk coffee. This is why we were not able to perform this analysis. Complex composition of coffee and the variety of social contexts underlying its consumption make the evaluation of its effects on laryngeal cancer very difficult. A possible effect of coffee consumption in laryngeal carcinogenesis could be reflux induction. Although gastro-oesophageal (laryngopharyngeal) reflux has not yet been confirmed as a carcinogenic cofactor, it is clear that reflux may cause acute and chronic laryngeal inflammation. The role of coffee drinking and reflux as a co-factor in laryngeal carcinogenesis remain to be investigated. Furthermore, coffee consumption could be a risk factor in patients who drink very hot coffee. Knowledge about the level of exposure to different coffee constituents may provide a deeper understanding of the real role of coffee in cancer risk (40).

This is the first study conducted in Montenegro with the aim to investigate the relative importance of the described risk factors of laryngeal cancer. Several limitations of our study must be acknowledged. The number of cases was small compared to some other case-control studies for this cancer. As in all case-control studies, recall and selection biases are of potential concern. It is also possible that dietary habits of hospital controls may differ from those of the general population. However, controls were selected among patients with admission diagnosis not related to tobacco smoking and alcohol drinking. Moreover, in order to reduce any information bias, the questionnaire was administered to both patients and controls by one interviewer and under similar conditions. The high response rate, both for controls and patients, is the strength of this study.

In conclusion, identification (and correction) of specific factors in susceptible patients with laryngeal squamous cell carcinoma may influence both the disease management and outcome. A great majority of laryngeal cancers could be prevented by elimination of tobacco smoking and reduced alcohol consumption. Further studies are needed to investigate the effects of passive smoking, coffee consumption, and diet.

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**Sažetak**

## FAKTORI RIZIKA OD KARCINOMA LARINKSA U CRNOJ GORI

Maligni tumori larinksa najčešći su tumori glave i vrata. Glavni faktori rizika od razvoja malignih tumora grkljana su pušenje i konzumiranje alkoholnih pića.

Cilj rada bio je ispitivanje potencijalnih faktora rizika od nastanka malignih tumora larinksa.

Sprovedena je studija slučaj-kontrola. Studijsku grupu činilo je 108 pacijenata s histološki verificiranim rakom larinksa i 108 kontrola individualno izjednačenih po spolu, dobi ( $\pm 3$  godine) i mjestu stanovanja. Svi ispitanici su anketirani ciljanim epidemiološkim upitnikom a u analizi podataka korištena je multivarijantna logistička regresijska analiza.

Koristeći se multivarijantnom logističkom regresijskom analizom, statistički značajnu povezanost s rakom larinksa dobili smo za sljedeće varijable: konzumiranje žestokih pića (omjer izgleda /OR/=2.93, interval pouzdanosti /CI/ 95 % = 1.17 do 7.31), konzumiranje više od 2 alkoholna pića na dan (OR = 4.96, CI 95 % = 2.04 do 12.04), konzumiranje cigareta duže od 40 godina (OR = 4.32, CI 95 % = 1.69 do 11.06), konzumiranje više od 30 cigareta na dan (OR = 4.24, CI 95 % = 1.75 do 10.27), konzumiranje više od 5 šalica kave na dan (OR = 4.52, CI 95 % = 1.01 do 20.12) i konzumiranje gaziranih pića (OR = 0.38, CI 95 % = 0.16 do 0.92).

Obolijevanje zbog malignih tumora larinksa moglo bi se značajno smanjiti prestankom konzumiranja duhana i alkohola.

**KLJUČNE RIJEČI:** *alkohol, case-control studija, duhan, gazirana pića, grkljan, kava, pušenje, rak*

## CORRESPONDING AUTHOR:

Elvir Zvrko, MD, M.Sc.  
Klinika za ORL i MFH  
Klinički centar Crne Gore  
81000 Podgorica, Montenegro  
E-mail: [elvirez@cg.yu](mailto:elvirez@cg.yu)